viruses, (enteric cytopathogenic human orphan (ECHO) viruses (types 9 and 22), influenza A and B, mumps, measles, rubella, variola, vaccinia, hepatitis, adenoviruses, Epstein-Barr virus, cytomegalovirus and varicella-zoster virus.[9,15]

Heart disease has been experimentally reproduced in mice with Coxsackie virus A-9 and B3 viruses,[16] and in adult monkeys, with Coxsackie B-4 virus which produced pancarditis, resembling rheumatic heart disease with valvulitis and myocarditis.[11,17] In adult mice, Coxsackie A-9 virus produced benign heart disease. In young mice, Coxsackie B3 virus caused virulent myocarditis with progressive myocardial injury. The severity of experimental virus infections was increased by factors such as exercise, hydrocortisone, undernutrition, alcohol, pregnancy and virulence of the infecting virus.[16]

Viral involvement of the heart may lead to a wide spectrum of clinical illness:[18,19]

- Symptoms of acute pericarditis.
- Chest pain mimicking myocardial infarction.
- Progressive congestive heart failure.
- A nonspecific influenza-like illness with fever, headache, muscle or joint pains and headache.

Relapses may occur, especially in patients presenting initially with symptoms of acute pericarditis. A history of antecedent viral syndrome with fever, headache, muscle pain, pleural effusion or pneumonitis, and absence of recent angina pectoris help to differentiate myopericarditis from coronary heart disease.

Coxsackie B viruses[18,19] have been recognized as the most common viral agents in pericarditis, either by demonstration of antibody rise or by isolation of virus from stool, throat or pericardial fluid. Other viruses have been incriminated usually only serologically. Other known infectious agents and other causes such as chest trauma; toxins; neoplasia; collagen vascular, hormonal and metabolic diseases need to be excluded by appropriate studies. In most cases, a specific cause cannot be, however, identified. In order to understand the cause of idiopathic cases of myopericarditis, it is helpful to remember that in experimental disease in mice, infectious virus is commonly present in excretions and heart tissue only during the incubation period and in the acute stage of the disease.[20] The presence of antibodies to the heart muscle and virus antigen in the heart may be the only remaining trace of virus activity in chronic noninfectious phase.

High prevalence of elevated neutralizing antibodies to Coxsackie group B viruses[21] decreases their diagnostic value. Demonstration of immunoglobulin M (IgM) type-specific antibodies to Coxsackie B viruses may help to establish an etiological diagnosis in those cases of myopericarditis where the usual diagnostic techniques fail.[22]

Patients with viral myopericarditis should be treated with complete bedrest. Mice infected with Coxsackie B viruses which were forced to swim for their life invariably died with enlarged hearts, whereas the heart size remained normal if they were allowed to rest.[23] The use of corticosteroids is controversial. In animal studies, corticosteroids administered during the acute phase of Coxsackie virus infection enhanced virus titers and lesions.[24] In the experience of some clinicians, however, steroids appear to be life-saving in later stages of the disease if the patient is developing heart failure in spite of full bedrest and digitalization.[25]

Tuberculous and Fungal Pericarditis

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THERE IS CONSIDERABLE MERIT in including tuberculous pericarditis and fungal pericarditis in a conjoint discussion of these entities since they share many common features when affecting the human host. Both entities have similar pathogenesis, pathological findings, and in many instances, a clinical presentation by history, physical examination, x-ray findings and physiological alterations, that precludes the separation of tuberculous pericarditis from fungal pericarditis. Moreover, both categories of disease are usually accompanied by the development of cutaneous hypersensitivity to the specific infectious agent. Furthermore, the management of tuberculous

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pericarditis and fungal pericarditis, as well as their complications, embodies similar therapeutic principles and techniques. Differences arise mainly in the form of antimicrobial therapy which is dependent on the specific infectious agent, as well as differences in incidence and prognosis of these infections as currently observed.

In general, this form of pericarditis is a chronic, insidious and progressive form of inflammation, making it impossible to document its duration. On occasion, tuberculous and fungal pericarditis present as acute, rapidly progressive purulent pericarditis.[26] The clinical presentation is characterized by the symptoms and signs of pericardial inflammation (precordial chest pain, fever and pericardial friction rub) as well as associated hemodynamic dysfunction. Less frequently, because of the insidious course of this form of pericarditis, only the hemodynamic consequences of the restrictive cardiac defect may be evident (jugular venous distension, hepatic congestion, ascites and peripheral edema). When the pericarditis is associated with concurrent inflammation of contiguous structures within the thorax—which include lesions within the endocardium, myocardium, other mediastinal structures, pleura, lung, chest wall or diaphragm—or if the pericarditis occurs as part of a disseminated infectious process, the clinical presentation will be varied, reflecting the altered morphology and function of the affected organs. With increasing frequency, this form of pericarditis, particularly of fungal origin, appears during the course of a primary disorder, usually neoplastic or lymphomatous, which can obscure the infectious nature of the pericarditis.

Cause

The mycobacterium responsible for tuberculous pericarditis, identified by culture or guinea pig inoculation, has been the human variety, Mycobacterium tuberculosis.[27] Although the various atypical mycobacteria are capable of producing pathologic changes that are indistinguishable from M tuberculosis, their presence in pericardial lesions is unknown. In view of the growing interest and knowledge concerning atypical mycobacteria, it is reasonable to anticipate atypical mycobacteria will be cultured in a patient with tuberculous pericarditis, albeit a remote possibility.

The species of fungi that have been recovered from pericardial lesions are numerous. These can be separated into the pathologic fungi responsible for the systemic mycoses in the otherwise healthy host, and the opportunistic fungi which become invasive as a result of an alteration in the defense mechanisms or bacterial flora of the host. In the former group, Histoplasma capsulatum,[28-30] Coccidioides immitis,[31] cryptococcus,[32] blastomyces,[33] actinomyces[34] and nocardia,[35,36] have been isolated either from the pericardial exudate or from tissue biopsy specimens. In the latter group, candida and aspergillus have been recovered,[37] usually as part of a generalized infection in the immunologically impaired host.

The frequency with which these infectious agents have been associated with pericarditis has increased considerably during the past two decades. Before that time, the most common cause of granulomatous pericarditis was tuberculosis, accounting for 20 percent of all forms of pericarditis.[38,39] With effective tuberculosis control, resulting from increasing efforts in the detection, drug treatment and prevention of tuberculous infection, the incidence of tuberculous pericarditis has been significantly reduced. In those areas of the world where tuberculous infection remains prevalent and less well controlled, tuberculosis remains the most common cause of infectious pericarditis.[41]

Pericarditis due to the pathogenic fungi occurs infrequently and sporadically, constituting approximately 1 percent of all forms of pericarditis. Because of the magnitude of histoplasmosis in the United States, it is not surprising that histoplasmosis is the most common fungal agent responsible for granulomatous pericarditis and constrictive pericarditis, particularly in the great river valleys where histoplasmosis is endemic.[42-44] Likewise, sporadic cases of coccidioidomycosis with pericarditis are recognized primarily in the southwestern portion of the United States and the northern states of Mexico, where this infection is endemic.

Of greater concern is the increasing frequency of pericarditis due to saprophytic fungi, as well as fungi of usually low virulence such as Nocardia asteroides. This can be attributed in large measure to specific therapeutic modalities which have been introduced or used with increasing frequency during the past several decades. These include broad spectrum antibiotics, corticosteroids, cancer chemotherapy and radiation therapy. Colonization of mucous membranes by saprophytic fungi with

subsequent systemic dissemination has been observed in association with use of these therapeutic modalities, frequently in combination. The reactivation of previously stable foci of fungal and mycobacterial infection has also been associated with the prolonged use of immunosuppressive agents. The increased practice of intravenous drug abuse has also contributed to a rising incidence of fungal infection associated with pericarditis.

Pathology

The initial histologic response to an acute tuberculous or fungal infection is a polymorphonuclear leucocytic infiltration. This can progress to frank suppuration with abscess formation. More commonly in tuberculosis, however, the original inflammatory response subsides, with an influx of plasma cells and lymphocytes and the formation of noncaseating granulomata. Surrounding these lesions is a fibrotic reaction, with the formation of collagen. Caseation necrosis is a later sign of the granulomatous response and may not appear until many months have elapsed since the initial infection. Calcification and further fibrosis occur after caseation.

The serial histologic responses to fungal infection encompass similar pathologic changes seen with tuberculous infection. Certain fungi, especially Blastomyces and Actinomyces species evoke a persistent suppurative response, with very little granuloma formation, while Histoplasma and Coccidioides species often have pathological changes indistinguishable from those caused by M tuberculosis. It is essential to obtain special stains for acid fast bacilli and fungi on all tissues removed for study, since these organisms are frequently not identified on routine histologic sections alone. Even in the absence of granuloma formation, special stains are essential to identify the etiologic agent.

In tuberculous pericarditis, the administration of antituberculosis chemotherapy for several weeks may be sufficient to significantly reduce or eliminate the organisms in biopsy tissue obtained at that time, so that acid-fast bacilli will not be observed in histologic sections. The granulomatous changes, on the other hand, heal more slowly and can be identified histologically for a protracted period of time while on chemotherapy. For the same reason, culture of the biopsy on appropriate media may successfully yield the infectious agent, despite its absence in histologic section.

Pathogenesis

The portal of entry for M tuberculosis, as well as the majority of the pathogenic fungi, is the respiratory tract. As part of the primary infection, not only is there a lobular pneumonitis within the pulmonary parenchyma, but characteristically there is dissemination through the lymphatic channels to the regional lymph nodes, both in the hilus of the infected lung and in the adjacent mediastinum. Frequently, the supraclavicular nodes are similarly affected. In addition, shortly after the initial infection, there is a generalized dissemination of the infectious agent through the blood stream, establishing secondary foci in many, if not all, body organs.

Most of the secondary foci, either by the lymphogenous or hematogenous dissemination, are clinically inapparent and together with the primary focus undergo spontaneous healing, but still contain viable tubercle bacilli or fungi. For reasons that are not clear, the inflammatory process within certain foci will continue to actively suppurate, caseate, and perforate into adjacent structures. It is primarily this mechanism that results in pericardial infection, namely, the extension of the inflammatory process into the pericardium from a strategically situated caseous hilar or mediastinal lymph node. Hematogenous seeding of the pericardium can occur not only during the initial course of the primary infection, but also as part of a late miliary dissemination, resulting in direct seeding of the pericardium or, more likely, the production of microabscesses in the subjacent myocardium which ultimately rupture into the pericardial space.

The saprophytic, as well as less virulent fungi, obtain access into the body through the mucosa of the body cavities and the gastrointestinal tract. Occasionally there is inoculation of the infectious agent into the skin, with later dissemination. Penetrating wounds of the thorax and surgical procedures on the heart, including pericardiocentesis, create potential pathways for the introduction of the infectious agent into the pericardium. Moreover, with the increasing incidence of intravenous drug abuse with complicating fungal endocarditis and myocarditis, extension of the infection into the pericardial space occurs. Penetration of a tuberculous or fungal abscess of the subphrenic space into the pericardium is conceivable but has not been documented. The appearance of tuberculous pericarditis or fungal

pericarditis following a pulmonary resection for disease due to these infectious agents has been observed.[45]

Diagnosis

In view of the varied clinical spectrum of pericarditis, it is essential to consider mycobacteria and fungi as possible etiologic agents promptly and without exception. Only by recovering the agent in culture, either from the pericardial exudate or identifying it with certainty by culture or histologic section of the pericardium, can a definitive diagnosis be made. Pericardiocentesis and pericardial biopsy by the intercostal or subxiphoid approach has been used for this purpose.[46] The pericardial fluid thus obtained is exudative in character, serous or serosanguinous in appearance, and contains varying numbers of inflammatory cells which reflect the state of inflammation of the pericardial surface. Appropriate cultures of the pericardial fluid for acid-fast bacilli are positive in only 25 percent of the patients with proven tuberculous pericarditis. While a lower yield of positive fungal cultures is obtained in the presence of fungal pericarditis, culture of tissue biopsy specimens will increase the diagnostic yield.

Often other methods must be used to establish a presumptive diagnosis of granulomatous pericarditis so that a reasonable therapeutic regimen can be initiated. These techniques include skin testing with appropriate antigens; serologic tests for fungi, both on pericardial fluid as well as blood serum; cultures of secretions or other areas of exudation or suppuration for acid-fast bacilli and fungi, and selected tissue biopsy for histologic section and culture.

Frequently, the presence of delayed skin test hypersensitivity to a specific microbial antigen indicates the presence of these microorganisms within the subject host, but does not differentiate between past and currently active disease. The conversion of a previously known negative reaction on a skin test to a positive one indicates that the infection by this microorganism was acquired during the interval between the two tests. Conversely, the reversion of a previously known positive reaction on a skin test to a negative one may indicate progressive dissemination by the infectious agent. In the presence of pericarditis due to tuberculosis, histoplasmosis and coccidioidomycosis, the intradermal test is positive to the appropriate antigen with a confidence of greater than 90 percent. Although coccidioidin antigen has greater specificity than other fungal antigens, occasional cross-reactions are seen using fungal antigens, making it necessary to correlate these findings with additional data.[47]

Of greater value in establishing the presumptive diagnosis of a specific fungal infection is the presence of a serological reaction to the fungal antigen.[48] To date, this has been accomplished with considerable confidence in coccidioidomycosis and histoplasmosis. The demonstration of precipitating antibodies in the serum, either to coccidioidin or to histoplasmin, is evidence for a recently acquired infection by the specific fungus. Precipitin antibodies have also been observed to appear during the chronic phase of illness when the infection spreads to a new serosal surface, such as pleura, pericardium or peritoneum. Complement fixing antibodies appear in the serum later in the course of the infection, particularly during the chronic phase of the disease. Rising titers of complement fixing antibodies indicate worsening of infection, while diminishing titers are consistent with control of the infection, making it a useful tool for guidance with specific antifungal chemotherapy.

Additional data supporting the presumptive diagnosis of granulomatous pericarditis is the identification of the infectious agent by culture of histologic technique in other organs or bodily secretions. Accordingly, the presence of acid-fast bacilli or fungi in the smears and cultures of sputum, pleural effusion or blood, or the identification of the microorganism in the lung, lymph node, liver or bone marrow—or in other sites of suppuration, granuloma formation or fistulous tracts—adds considerable support to the probability that this is the agent responsible for the pericarditis. It is important to emphasize that collection and incubation of these specimens under aerobic as well as anaerobic conditions are essential, since certain fungi, such as Actinomyces, grow best under anaerobic conditions.

Treatment

Therapeutic measures used in tuberculous or fungal pericarditis include:

- *General and supportive care.* This includes measures for the management of chest pain and pyrexia, as well as bedrest when cardiac output is impaired. In the presence of an underlying disease during which pericarditis has appeared, management of the primary disease is essential.
- *Control of the hemodynamic complications.*

The presence of cardiac tamponade resulting from a large pericardial effusion is relieved by prompt and adequate pericardiocenteses. During the early stages of effusive pericarditis, repeated pericardiocenteses may be required. If this problem cannot be controlled, corticosteroids should be added to the therapeutic regimen providing appropriate antimicrobial therapy has been started.

• *Pericardial suppuration.* In the event of an aggressive purulent pericarditis due to tuberculous or fungal infection, surgical drainage may be necessary should pericardiocenteses fail to control this problem. Adequate drainage has been achieved by the creation of a pericardial fenestration which is appropriately drained to the exterior.[49]

• *Tuberculous pericarditis.* If tuberculous pericarditis is suspected, albeit on meager clinical data, the prompt institution of antituberculosis chemotherapy, using two effective agents, such as isoniazid and ethambutol, is recommended. The therapeutic effectiveness and the virtual absence of adverse reactions to these drugs when used in recommended dosages,[50,51] balanced against the increased morbidity and significant mortality that result from delay in the treatment of tuberculous pericarditis, justify this approach.

• *Fungal pericarditis.* In the presence of pericarditis due to the common pathogenic fungi, as in histoplasmosis, coccidioidomycosis, cryptococcosis and blastomycosis, the intravenous administration of amphotericin B has been associated with successful management of the infection. In view of the difficulties involved with the administration of amphotericin B, including its frequent adverse effects, a definitive diagnosis or at least a strongly presumptive diagnosis of fungal pericarditis should be made before amphotericin B therapy. For candida infections, 5-fluorocytosine can be used. Penicillin is effective against Actinomyces species, while sulfonamides have been successfully used in nocardia infections. On occasion, the fungal pericarditis has responded satisfactorily to surgical drainage alone, but this is not recommended without specific antifungal chemotherapy.

• *Constrictive pericarditis.* For the patient in whom there is cardiac embarrassment associated with constrictive pericarditis, pericardiectomy must be considered.[52,53] Although this complication may appear relatively early in the course of granulomatous pericarditis, it is more commonly a late manifestation, appearing many months or years after the original infection. Approximately 50 percent of these patients will show pericardial calcification on conventional x-ray views of the heart in the region of the left ventricle. Tomographic studies may be required to better visualize this abnormality. The response to pericardiectomy is generally satisfactory, with improvement of cardiac output immediately after the operative procedure.[54] In certain patients, however, because of impaired contractility of the ventricles, the increased circulatory load which occurs following pericardiectomy cannot be tolerated, so that congestive heart failure rapidly supervenes.[55]

• *Corticosteroids.* The value of the anti-inflammatory action of corticosteroids in various forms of pericarditis has been well documented.[56] For the control of pain of pericardial origin that does not respond to conventional analgesics and the management of cardiac tamponade that cannot be controlled by repeated pericardiocenteses, corticosteroids have a distinct role in the adjunctive therapy of pericarditis. When an appropriate chemotherapeutic program has been instituted in tuberculous pericarditis, corticosteroids do not exert an adverse effect on the control of the infection. Caution should be observed in the administration of protracted corticosteroid therapy when the infectious agent has not been identified or the patient is not receiving specific antimicrobial therapy. A brief course of corticosteroids to achieve reversal of cardiac tamponade may be sufficient to control this problem, pending the institution of additional therapeutic measures.

The role of corticosteroids in preventing the development of constrictive pericarditis is moot. Some studies have suggested a significant reduction in the incidence of constrictive pericarditis since the advent of antituberculous chemotherapy, especially when an effective drug regimen is administered promptly following the recognition of the pericarditis. In general, the use of corticosteroids for this purpose has not been substantiated.

Summary

Tuberculosis and to a lesser degree systemic mycoses are associated with pericarditis. The incidence of tuberculous pericarditis, both in its effusive and constrictive forms, has been reduced with the control of tuberculosis since the advent of specific antituberculosis chemotherapy. Although tuberculous or fungal pericarditis is usually an indolent and insidiously progressive disease, it can present as an acute suppurative pericarditis.

Every reasonable effort should be made to identify the etiologic agent so that an appropriate therapeutic program can be initiated. Since the previously high mortality of tuberculous pericarditis has been remarkably reduced by the early administration of an appropriate drug regimen, this practice is recommended whenever tuberculous pericarditis is suspected. It is important to establish the diagnosis of a specific fungal pericarditis because of differences in antimicrobial chemotherapy. The indications for pericardiocentesis, corticosteroids, surgical drainage and pericardiectomy in the management of this form of pericarditis have been reviewed.

Bacterial Pericarditis

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THE CLINICAL signs and symptoms of bacterial (purulent) pericarditis are similar to those of the other forms of pericarditis except that the patients are usually more toxic and ill with rapidly changing hemodynamic abnormalities.

Bacterial pericarditis is an old disease first described in an animal by Galen in the first century and subsequently described in humans approximately a thousand years ago. The incidence of bacterial pericarditis from autopsy series before the antibiotic era was about 40 percent of all pericarditis;[57] subsequent to the antibiotic era the incidence has decreased to 10 to 20 percent.[57] Additionally, autopsy series showed that purulent pericarditis before 1945 was responsible for approximately 1 percent of all deaths.[57] Since 1945, however, the figure has been less than 1 percent.

The pathogenesis of bacterial pericarditis occurs through several mechanisms:

- *Contiguous spread from an adjacent pleuropulmonary infection.* Before the antibiotic era, most cases of purulent pericarditis were due to the pneumococci and this was invariably associated with pneumonia or empyema or both. The postulated pathophysiology has been that the adjacent pleuropulmonary infection may cause an inflammatory response in the pericardium with migration of neutrophils and eventual deposition of fibrin.[26,58,59] It has not been clear whether bacteria migrate directly from the lung tissue itself or there is subsequent bacteremia and invasion of the pericardial sac.

- *The hematogenous spread of bacteria from a distant focus to the pericardium.* Staphylococcal osteomyelitis is a common cause of purulent pericarditis and the pathogenesis is probably via hematogenous spread of the bacteria to pericardium. The exact mechanism is unknown. Animal experiments[60] suggest that an initial myocarditis or myocardial abscess develops. Bacteria then migrate (or rupture from the abscess) into the pericardium to form purulent pericarditis.

- *Direct inoculation of bacteria into the pericardial sac.* This may result from penetrating wounds to the pericardium or occur as a result of cardiac surgery.[57] There have been reports of bacterial pericarditis secondary to infective endocarditis.[61-63] Associated myocarditis with myocardial abscess formation probably permit migration of bacteria to the pericardial space.

The incidence of particular types of bacteria in purulent pericarditis is difficult to assess since most series include only a few case reports. However, a review of the world's literature up to 1959[26] of all cases of purulent pericarditis suggested staphylococci, pneumococci and streptococci as the predominant organisms. There were a moderate number of meningococci reported; since that report, the incidence has increased. In children under the age of two years, the cause of purulent pericarditis is similar to that in adults with staphylococci and pneumococci predominating, but Hemophilus influenza is also a common agent.[64] Hemophilus influenza should always be considered in the pediatric age group. Salmonella species may also cause bacterial pericarditis.[65] Most have been nontyphosal types with Salmonella typhimurium being the most common strain.

Pneumococcal pericarditis was the most common cause of purulent pericarditis before the antibiotic era. However, a recent review by Kauffman and coworkers[59] indicates that there have only been 15 cases of pneumococcal pericarditis reported since 1945. This is probably a reflection of penicillin therapy. Kauffman's group included five cases of their own in this report and it is in-

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